

REMARKS

These remarks are in response to the Office Action mailed December 24, 2003. Claim 13 has been amended to correct a typographical error. No new matter has been introduced. Applicant respectfully requests reconsideration and allowance of the pending claim.

I. DEPOSIT REQUIREMENT

The Office Action alleges that the deposit requirement for the SKG embryos (Accession No. BP-7790) is not satisfied in the present application. In particular, the Office Action alleges that Applicant has not provided a declaration indicating the chain of custody was maintained since the time of filing of the application.

Applicant respectfully submits that the Declaration filed April 17, 2003, clearly indicates at paragraph 5 that, "...the deposited material...was in our possession at the time of filing...and is the same as that described in the specification as the SKG strain." Furthermore, the Applicant has indicated that the deposited material will be replaced if viable samples cannot be dispensed by the depository (see, e.g., paragraph 6 of the Declaration filed April 17, 2003). Thus, Applicant submits that the declaration clearly indicates custody and possession of the deposited material as of the filing date of the present application. The specification has been amended to satisfy the deposit requirements and the deposit has been fully supported by declarations filed in the application. The deposit requirement is fully satisfied in accordance with 37 C.F.R. §1.801 et seq.

Applicant submits that the 5 types of mice referred to in the specification were obtained during the mating experiment to examine the fashion in which the gene causative of the arthritis is inherited. The details of the experiments and mice described in Example 1 are explained below.

Example 1 of the specification shows the experiments carried out from about 1993. The mating experiment (hereinafter, this mating experiment is referred to as "the first mating experiment") was performed to examine the properties of the gene causative of the natural onset of the autoimmune arthritis identified in the mouse strain deposited as BP-7790. The first mating

experiment is disclosed at page 4, lines 24 to 29 and page 5, lines 1 to 17. In the first mating experiment, the 1st, 2nd and 3rd generation mice were obtained from the female mouse with joint swelling identified in Applicant's mouse population in 1993.

Later experiments were carried out to observe the inheritance of mice obtained in the first mating experiment and is disclosed at page 5, lines 22 to 29 and page 6, lines 1 to 3. A further experiment was carried out in a large scale and is disclosed at page 6, lines 3 to 10. In this experiment, it was confirmed that the gene causative of the natural onset of the autoimmune arthritis is an autosomal and recessive gene.

In "the first mating experiment" above, five types of mice are disclosed and described in the specification as follows:

- BALB/c mouse and Founder - "In 1993, a female mouse with joint swelling (the founder) was found in an inventor's BALB/c colony (BALB/e mouse) (purchased in 1992 from Nippon SLC).";
- 1st generation - "The SKG mouse having developed arthritis was mated with a BALB/c mouse (originally purchased from Nippon SLC). As the result of this mating, 12 mice were obtained (1st generation), among which 4 mice showed joint swelling (the incidence of arthritis 33%)."
- 2nd generation - "One mouse was arbitrarily selected from the mice having joint swelling and mated again with a BALB/c mouse in a mouse colony (originally purchased from Nippon SLC) maintained in the inventor's laboratory. As the result of this mating, 15 mice were obtained (2nd generation), among which 6 mice (4 females and 2 males) had joint swelling (the incidence of arthritis 40%)."
- 3rd generation - "One mouse was arbitrarily selected from the mice having joint swelling and mated again with another mouse in the above-described BALB/c colony. As the result, 28 mice were obtained (3rd generation), among which 10 mice had joint swelling (the incidence of arthritis 35%)."
- In addition SKG mice maintained as homozygotes are disclosed - "The SKG mice are therefore maintained at present as homozygotes. Their incidence of arthritis is

almost 100%, and the penetrance of the genetic abnormality in the homozygous is considered to be almost 100% in the environment where they are currently maintained."

The inventor's colony was maintained by mating mice among the colony. In the Declaration under 37 C.F.R. §132 filed on February 1, 2001, the history of the inventor's BALB/c colony was described as follows:

The BALB/c mouse colony from which the SKG strain originated was maintained for nearly one and a half years before a female mouse with joint swelling was found by the inventor. In this mouse colony, usually one to two males and four females were kept in a cage, and five such cages for breeding were maintained to produce BALB/c mice. When female mice became pregnant in these cages, they were separated to a single until they gave birth and then weaned the offspring. Next, breeding pairs (two males and four females) were prepared from these offspring. Because the BALB/c mice thus produced were used for immunological experiments, their health status was occasionally checked by visual inspection, serological check of autoantibodies, and radiographic and histological examination. The inventor selected this particular breeding strategy to make it possible to detect recessive mutations if the phenotype of the mutation can be detected. When the joint-swollen female mouse was detected, it was isolated. This initial "SKG" female mouse with joint swelling was subsequently bred with another apparently normal male mouse in the colony. Their offspring developed similar joint swelling thus, the genetic inheritance of the joint swelling phenotype was first considered to be autosomal dominant because this first set of offspring developed joint swelling. It turned out later that the male mouse itself bore the mutation. i.e. the mutation was already shared by other mice in the same colony. Although the incidence of arthritis in these offspring was first estimated to be about 30% when assessed at three months, it was determined that at the third generation, when the offspring from joint swollen female and male mice were kept observed until 6 months of age, all of them developed arthritis. This difference was mainly because I first did not notice swelling of small finger joints and only counted advanced arthritis in large joints. From the third generation to the present generation (now maintained as more than 5 generations), the phenotype of the SKG strain has been stable in terms of the incidence and the severity of the arthritis.

As described above, Applicant maintained the colony through selective breeding and artificial crosses to detect a mutation. The deposited mouse strain was developed through non-natural selective breeding and selective crosses in an effort to detect a gene mutation. As such

the incidence of the mutated gene giving rise to autoimmune arthritis was gradually increased in the Applicant's colony.

In general, the repeated backcrosses and brother-sister matings resulted in a mouse in which the mutated gene is maintained stably and homozygously. Originally, the first mating experiment disclosed in Example 1 of the specification was carried out to estimate the fashion in which the gene causative of the arthritis was inherited and was not performed to produce mice that stably inherited the gene causing autoimmune arthritis. The experiment that was carried out to produce the genetically stable mice was "the later experiment which resulted in the stable mice" disclosed at page 6, lines 3 to 10. The inventor's declaration above states, "From the 3rd generation to the present generation (now maintained at more than 5 generations), the phenotype of the SKG strain has been stable in terms of the incidence and the severity of the arthritis." This indicates that approximately ten generations are needed to produce the stable mouse strain.

The specification describes, "In 1993, a female mouse with joint swelling was found in an inventor's BALB/c colony (purchased in 1992 from Nipon SLC) in the Institute for Physical and Chemical Research. This joint swelling was assumed to be due to a genetic mutation; and this mutant strain was designated as SKG." (see, e.g., page 4, lines 24-29 of the specification). As described above, one female mouse, which had the gene causative of the arthritis (homozygously), was found by the inventor. The inventor designated the mouse as SKG strain provisionally at that time. It was in "the later experiment which resulted in the stable mice" that the stable SKG strain was conclusively produced by the inventor.

The deposited mouse embryos were obtained from the mice of "the later experiment which resulted in the stable mice", of which incidence of arthritis is almost 100%, and the penetrance of the genetic abnormality in the homozygous mouse is considered to be almost 100%. Regarding "the later experiment which resulted in the stable mice", the specification describes, "By later experiments on the inheritance in a large scale, it was reasonably estimated that the genetic abnormality causing the natural onset of autoimmune arthritis is autosomal and recessive. The inventor carried out more than ten consecutive backcrosses and brother-sister matings between the offspring originated from the inventor's colony, which developed the

autoimmune arthritis and the mouse arbitrarily selected from the inventor's colony. Considering the way to maintain the inventor's colony described in the inventor's declaration above, it is deduce that almost all mice in the inventor's colony had the gene causative of arthritis homozygously at the time when "the later experiment which resulted in the stable mice" was carried out. Of course, when this experiment was carried out, the joint swelling in the small joints were taken into account. It was after "the experiment which resulted in the stable mice" that the inventor confirmed that the SKG mice had the gene causative of arthritis stably and homozygously. The SKG mice are therefore maintained at present as homozygotes. Their incidence of arthritis is almost 100%, and the penetrance of the genetic abnormality in the homozygotes is considered to be almost 100% in the environment where they are currently maintained." (see, e.g., page 6, lines 3 to 10).

Therefore, the mice described in the specification as, "The SKG mice are therefore maintained at present as homozygous. Their incidence of arthritis is almost 100%, and the penetrance of the genetic abnormality in the homozygous mouse is considered to be almost 100% in the environment where they are currently maintained," was the SKG strain mice that were deposited. The inventor maintained the genetically stable mice and deposited them as ATCC accession No. BP-7790.

According to Mendelism, the incidence of arthritis in the 1st, 2nd and 3rd generation mice is predicted and dependent of the genotype of the mated mouse, and high genetic penetrance of the mutated gene.

<u>Founder and the mated mouse among 1st, 2nd and 3rd generations</u>	<u>Mouse mated with the founder</u>	<u>Incidence of Arthritis</u>
Homozygous	Homozygous	100%
	Heterozygous	50%
	No mutated gene	0%

The incidence of arthritis of 1st, 2nd and 3rd generation mice in the first mating experiment was neither 50% nor 100%. It can be said at least that the mouse arbitrarily selected from the Applicant's colony had the mutated gene causative of the arthritis, irrespective of homozygously or heterozygously. This shows that the mutated gene frequency increased in the Applicant's colony at the time when the first mating experiment was carried out. As described above, the

gene causative of the arthritis is an autosomal and recessive gene. In "the first mating experiment" above, the female BALB/c mouse with joint swelling was mated with other mice selected from Applicant's colony. The initial female mouse found in Applicant's colony was apparently homozygous for the gene causative of the natural onset of the autoimmune arthritis since the homozygous gene causative of the natural onset of the autoimmune arthritis results in the phenotype that exhibits the natural onset of the autoimmune arthritis. The colony was selectively mated by Applicant such that the mutated gene frequency was increased in the colony and mice which were homozygous for the gene causative of the natural onset of the autoimmune arthritis became prevalent in the colony. This is partly due to the inventor's awareness of swellings of small joints.

The genotype of the gene causative of the natural onset of the autoimmune arthritis and the phenotype of BALB/c mouse, the founder, 1st, 2nd and 3rd generation mice, and the SKG mice were as follows. The genotype is expressed as set forth below.

Genotype +/+:	homozygous of wild type gene
Genotype +/-:	heterozygotes
Genotype -/-:	homozygous of mutated gene

"+" denotes the wild type gene relating to the development of the natural onset of the autoimmune arthritis and "-" denotes the mutated gene relating to the development of the natural onset of the autoimmune arthritis. An individual having the genotype of "-/-" develops the natural onset of the autoimmune arthritis since the gene is autosomal and recessive gene.

Type of mice	Genotype	Phenotype
BALB/c	+/+	no symptoms
Founder	-/-	autoimmune arthritis
1st generation mice	-/-	autoimmune arthritis
	+/-	no symptoms
2nd generation mice	-/-	autoimmune arthritis
	+/-	no symptoms
3rd generation mice	-/-	autoimmune arthritis
SKG mice (deposited)	-/-	autoimmune arthritis

Regarding the 1st, 2nd and 3rd generation mice, 3rd generation mice were proved to have the mutated gene homozygously since further experiments revealed that all the mice developed autoimmune arthritis.

Applicant provides the attached *Nature* article that described the SKG mouse of the disclosure. In the reference, the gene causative of the natural onset of the autoimmune arthritis of SKG mice is identified. The *Nature* reference describes the point mutation at nucleotide 489 in the ZAP-70 gene is causative of the autoimmune arthritis of the SKG mouse (see, e.g., page 455, left column line 1 to page 456, left column last line). It was confirmed that the gene is inherited in an autosomal recessive fashion (see, e.g., page 454, lines 47-49, right column), which further provides proof of Applicant's invention as described in the specification.

Furthermore, the reference provides further evidence in support of Applicant's disclosure, namely the properties of the autoimmune arthritis. Figure 1j on page 455 shows the time course of joint swelling in the SKG mice. "Scoring of joint swelling" on page 459 of the reference shows the meanings of the scoring indicated in Figure 1j as "0, no swelling; 0.1, swelling of one finger joint; 0.5, mild swelling of wrist or ankle; 1.0, severe swelling of wrist or ankle." Referring Figure 1j, some mice do not develop joint swelling at all and some mice develop only swelling of fingers until 12 weeks old. After 16 weeks old, all mice develop swelling of large joints. The time course of joint swelling of Figure 1j supports the disclosures of the specification.

Applicant provides the attached Figure to further illustrate the history of the establishment of the SKG mice. Furthermore, Applicant has maintained the colony originated from the normal BALB/c mice colony to detect a gene mutation. The Applicant's effort for over a year and a half produced the female mouse with joint swelling due to a genetic mutation. The Applicant established the mice having the mutated gene stably and homozygously by non-naturally occurring backcrosses. The Applicant deposited mouse embryos from mice confirmed to have the gene causative of the arthritis stably and homozygously. The 3rd generation mice are substantially and genetically the same with the SKG mice that were deposited.

The examiner states on page 3 of the Office Action that the declaration does not fulfill the deposit requirement by providing which of the numerous mice disclosed in the specification (i.e. BALB/c mice, the founder mouse, 1st generation, 2nd generation, and 3rd generation), having different genotypes and different symptoms of arthritis that were specific to the genotype, were used to make the SKG strain deposited as BP-7790 in the third paragraph. The examiner also alleges that those mice described on page 3, lines 6-7 of the specification fail to teach that the SKG strain had rheumatoid arthritis or genes that cause natural onset of arthritis as claimed.

As described in the explanation above, the mice deposited were the mice that were maintained as homozygotes, of which incidence of arthritis is almost 100%. The penetrance of the genetic abnormality in the homozygous is considered to be almost 100%. Regarding the declaration indicating the chain of custody was maintained since the time of filing, Applicant provides herewith a further declaration to show that the chain of custody was maintained since the time of filing based on the explanation of the SKG mice above.

The examiner states, “. . .the applicant's argument (the backcrosses described in the specification were provided to show allelic variance. The deposited embryos comprise the SKG strain and not the backcrosses based on the SKG strain) is not persuasive. It cannot be determined that the backcrosses are “based on” the SKG strain rather than the backcrosses being used to make the SKG strain. It cannot be determined from applicants arguments which of the 5 strains described on pg 3, lines 1-7, is the SKG strain or was deposited as BP-7790 as claimed. Nor is it readily apparent which mouse described in the specification is the SKG strain.”

Applicant has described in detail the custody and crosses performed as well as the genetic traits and phenotypic traits of the mice above, which are supported throughout the specification as filed. The Office Action indicates that the statement “. . .in later experiments, the BALB/c mice considered to be normal and apparently free of swelling in large joints. . . The specification states the incidence of arthritis was 100% taking into account large or small joint arthritis. . .” is assumed to refer to BALB/c mice. The “BALB/c mice” disclosed in the above statement are the mice which were used in the mating with the mice having the arthritis and the “BALB/c mice” were picked from the Applicant's colony. The Applicant maintained the

BALB/c colony to detect a gene mutation. As apparent from the explanation above and Figure 1 attached herewith, from the time of the first experiment the mutated gene frequency has increased in the Applicant's colony. Thus, the genetic variance of the Applicant's colony became different from the normal BALB/c colony through non-naturally occurring backcrosses.

The examiner also alleges in "Summary of the invention" that the specification does not describe which generation of mice are the SKG strain, which mice were used to make the embryos deposited as BP-7790, or the genotype/phenotype of the SKG strain or the mouse strain deposited as BP-7790. As repeatedly indicated and described in the specification, the SKG strain and the deposited mouse embryos are those mice maintained as homozygotes and having an incidence of arthritis of ~ 100%, and the penetrance of the genetic abnormality in the homozygous is considered to be ~ 100%. These mice were used to make the embryos deposited as BP-7790.

II. REJECTION UNDER 35 U.S.C. §101

Claim 13 is rejected under 35 U.S.C. §101 as allegedly claiming non-statutory subject matter. In particular the Office Action alleges that the "mouse in claim 13 is a naturally occurring product." Applicants respectfully traverse this rejection.

As described in the specification and throughout the file history, the mouse deposited as accession no. BP-7790 was produced by the Applicant through non-naturally occurring mating and backcrosses. The gene causative of the natural onset autoimmune arthritis is maintained homozygously in the mice obtained from the deposit and as described in both the present specification and the attached article (Nature 426(6965):454-460, 2003). Applicant submits that the claimed mice obtained from the deposited embryos are not naturally occurring as the mice have been specifically bred and thus are removed from nature in a substantially isolated form. Accordingly, the claimed mouse is not a naturally occurring product as one cannot simply breed any two BALB/c mice and obtain Applicant's invention.

III. REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claim 13 stands rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) at the time the application was filed had possession of the claimed invention. The Office Action also alleges the claim 13 lacks written description. Applicant respectfully traverses this rejection.

Applicant respectfully submits that Examiner Sorbello of the U.S. Patent Office indicated in the Office Action mailed April 30, 2002, that the application is “enabling for a mouse strain SKG from BALB/c mouse. . . .” (see, e.g., page 4 of the April 30, 2002, Office Action). Examiner Kerr of the U.S. Patent Office indicated in the Office Action mailed April 25, 2001, that the application is “enabling for an SKG BALB/c mouse strain that develops natural onset rheumatoid arthritis. . . .” (see, e.g., page 5 of the April 2001, Office Action). Applicant has deposited SKG mouse embryos as indicated by the Declarations and the specification. Applicant has indicated a chain of custody (see, e.g., paragraph 5 of the Declaration filed on April 17, 2003), and indicated that the deposit shall be made available and that should the viability of the deposit be in doubt that such embryos will be replaced by Applicant (see, e.g., paragraph 6 of the April 17, 2003, Declaration). A biological deposit is *prima facie* evidence of satisfaction the enablement requirement. The availability of the biological product via a public depository provides an acceptable means of meeting the written description and the enablement requirements of 35 U.S.C. §112, first paragraph. MPEP §2164.06(b); *In re Argoudelis*, 434 F.2d 1390, 168 USPQ 99 (CCPA 1970); *Enzo Biochem. Inc. v. Gen-Probe Inc. et al.*, 296 F3d 1316 (Fed. Cir. 2002) (“*Enzo II*”). To satisfy the enablement requirement a deposit must be made “prior to issue” but need not be made prior to filing the application. *In re Lundak*, 773 F.2d 1216, 227 USPQ 90 (Fed. Cir. 1985).

Applicant submits that two prior Examiners found the specification enabling for what is now claimed. Furthermore, a biological deposit has long been recognized to satisfy the enablement requirement and more recently, the Federal Circuit in *Enzo II* stated,

In light of the history of biological deposits for patent purposes, the goals of the patent law, and the practical difficulties of describing unique biological materials in a written description, we hold that reference in the specification to a deposit in a public depository, which makes its contents accessible to the public when it is not otherwise available in written form, constitutes an adequate description of the deposited material sufficient to comply with the written description requirement of § 112, 1.

Applicant has satisfied the deposit requirements and provided evidence, by Declaration (filed April 17, 2003), that the SKG mice (recognized as being enabled for arthritis) were in fact the mice deposited and given accession no. BP-7790. Thus, the claimed subject matter is enabled and satisfies the written description requirement. Accordingly, Applicant respectfully requests withdrawal of the §112, first paragraph rejection.

IV. REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claim 13 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. More particularly the Office Action alleges the specification does not describe the genotype or phenotype of mice from an embryo deposited as BP-7790. Applicants respectfully traverse this rejection.

Applicant submit that the SKG mice are described in the specification and have been deposited and given accession no. BP-7790. The SKG mice are described in the specification at page 3, lines 4-7 as, “. . . a mouse strain having the character of natural onset of autoimmune arthritis.” The specific phenotype displayed by the SKG mice is further described throughout the specification at, for example, page 3, line 8 to page 4, line 12, and in the figures. Thus, Applicants submit that the phenotype of the SKG mice is set forth in the specification.

Furthermore, as recognized in *Enzo Biochem. Inc. v. Gen-Probe Inc. et al.*, 296 F3d 1316 (Fed. Cir. 2002), “for biological inventions for which providing a description in written form is not practicable, patentees may comply with the written description requirement by publicly depositing the biological material”. Applicant has deposited the SKG mice as previously discussed. Thus, Applicant has described the phenotype of the mice and satisfied the written

description by depositing the SKG mice. Accordingly, Applicant requests withdrawal of the §112, second paragraph rejection.

V. REJECTION UNDER 35 U.S.C. §102

Claim 13 stands rejected under 35 U.S.C. §102 as allegedly anticipated by Nordling (*Arthritis and Rheumatism*, 35:717-722, 1992). Applications respectfully traverse this rejection.

Nordling describes the spontaneously occurring arthritis in male DBA/1 mice. As the Examiner points out in Table 1 of Nordling, Nordling discloses BALB/c male mice. However, Nordling describes at page 717, first column line 14 to the second column line 2, "the susceptibility appears to be dependent on both sex-linked and non-sex-linked genes." Furthermore, the arthritis occurs only in male DBA/1 mice. This is contrary to Applicants deposited mice, which show that the gene associated with arthritis is autosomal and recessive (see, e.g., page 6, lines 3-6; see also, the attached Nature paper – *Nature*, 426(6965):454-460, 2003). All the SKG mice described in the specification developed arthritis irrespective of sex. As Example 9 of the present specification indicates, the occurrence of arthritis in SKG mice is related to T cells. However, T cells are not related to arthritis of DBA-1 mice (Hansson et al., *Arthritis and Rheumatism*, 43:844-851, 2002; attached hereto). Recently, it is thought that the arthritis that occurs in DBA/1 mice is not rheumatoid arthritis but another arthritis (Lories et al., *Ann. Rheuma. Dis.* 63:595-598, 2004; attached hereto). These findings also support that SKG mice are different from DBA/1 mice. Therefore, the SKG mice having accession BP-7790 as set forth in claim 13 are different from the mice disclosed in Nordling. Accordingly, Applicant respectfully requests withdrawal of the rejection under §102.

The Office Action further rejects claim 13 as allegedly anticipated by Yamanaka et al. (U.S. Patent No. 4,950,741). Applicant respectfully traverses this rejection.

Yamanaka et al. is related to a protein specifically found in the plasma of a human patient suffering from rheumatoid arthritis. Yamanaka et al., never describes that the rheumatoid arthritis occurs in mice. In Yamanaka et al. BALB/c mice are used for immunization with the

Applicant : Shimon Sakaguchi
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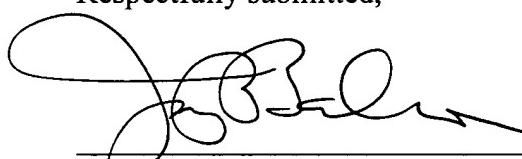
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protein to obtain an antibody against the protein. The antibody is intended to be used to detect the protein (See Example 4). Yamanaka et al. discloses a conventional method to obtain a monoclonal antibody against a protein by using mice such as BALB/c mice. An antibody against any protein can be obtained by immunizing ice with the protein. The monoclonal antibody generated in mice is not related to rheumatoid arthritis of the mice per se. Yamanaka et al. never discloses mice having characteristics of rheumatoid arthritis. Accordingly, Applicant respectfully requests withdrawal of the §102 rejection.

Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: 5/24/04


Joseph R. Baker, Jr.
Reg. No. 40,900

Fish & Richardson P.C.
PTO Customer No. 20985
12390 El Camino Real
San Diego, California 92130
Telephone: (858) 678-5070
Facsimile: (858) 678-5099